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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,262	02/05/2005	William Malcolm Charles Rosenberg	3769.1000-000	3832

21005 7590 09/05/2007

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ART UNIT	**PAPER NUMBER**
1637	

MAIL DATE	DELIVERY MODE
09/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/501,262	ROSENBERG, WILLIAM MALCOLM CHARLES
	Examiner	Art Unit
	Angela Bertagna	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-37* is/are pending in the application.

4a) Of the above claim(s) *1-15,21,26,34 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,18-20,22-25,27-33,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/12/05; 7/9/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II, claims 16, 18-20, and 22-30 on June 18, 2007 is acknowledged. Applicant's further election with traverse of SEQ ID NO: 1-3, 6, and 7 in the reply filed on June 18, 2007 is acknowledged. Applicant's arguments (see page 3) were found persuasive with regard to the examination of SEQ ID NO: 1 and 7 together. SEQ ID NO: 1 and SEQ ID NO: 7 will be examined together. Applicant's proposed restriction between the sequences (see page 4) was also found persuasive. SEQ ID NO: 1, 2, 3, 6, and 7 will be examined. Claims 16, 18-20, 22-25, 27-33, and 35-36 are readable on this combination of oligonucleotides.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-15 and 21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made without traverse in the reply filed on June 18, 2007.

Claims 26, 34, and 37 and also the nonelected sequences (SEQ ID NO: 4, 5, and 8) are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 18, 2007.

Priority

2. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Information Disclosure Statement

3. Applicant's submission of an Information Disclosure Statement on August 12, 2005 and July 9, 2004 is acknowledged. Signed copies are enclosed.

Specification

4. The disclosure is objected to because of the following informalities:

(1) The specification recites nucleic acid sequences greater than 10 nucleotides in length that are not identified by the appropriate SEQ ID NO: at pages 6-10, 14, 15, 17, and 19.

(2) The "Brief Description of the Drawings" heading is missing.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 18-20, 35, and 36 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are directed to products of nature, specifically nucleic acids. Amendment of the claims to indicate that the claimed oligonucleotide primers and probes are "isolated and purified" would overcome this rejection.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 16, 18, 22, 23, 25, and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Weimer (US 6,248,526 B1).

Regarding claim 16, Weimer teaches a kit for detecting HCV-1 in a sample comprising a primer that specifically anneals to the 5' noncoding region (see Example 1 at column 6, lines 1-29, where SEQ ID NO: 1-3 taught by Weimer anneal to the 5' noncoding region of HCV). Weimer teaches packaging these reagents in a kit at column 5, lines 50-60.

Regarding claim 18, Weimer teaches an oligonucleotide suitable for use in an amplification reaction comprising SEQ ID NO: 3 (see Example 1, column 6, lines 1-29, where SEQ ID NO: 1 comprises the instant SEQ ID NO: 3). Also, see the following alignment.

```
Qy          1 CGTCTAGCCATGGCGTTAG 19
              ||||||||||||||||||
Db          2 CGTCTAGCCATGGCGTTAG 20
```

Regarding claim 22, the primer taught by Weimer allows for amplification by PCR or RT-PCR (see Example 1, column 6, lines 1-29).

Regarding claims 23 and 25, Weimer teaches design of primers that target a conserved region of a virus such as HCV (column 5, lines 3-7 teach primer design from conserved regions; column 6, lines 1-29 teach amplification using SEQ ID NO: 1 as a primer, which targets a conserved region of HCV; column 5, lines 50-60 teach kits comprising the disclosed primers and amplification reagents). SEQ ID NO: 1 of Weimer is a universal primer suitable for isolating HCV from all HCV genotypes.

Regarding claim 29, Weimer teaches that the kit further contains reagents sufficient for detection by fluorescence where specific amplification of HCV causes fluorescence of a probe (see Example 1, lines 1-29 and the sequence listing where Weimer teaches that amplification of HCV results in release of the 3' quencher from SEQ ID NO: 1, thereby permitting detection of the FAM moiety at the 5' end of the sequence; see also column 5, lines 11-40 for further description of the fluorescence detection and column 5, lines 50-60, which teaches packaging of the reagents into kits).

8. Claim 18 is rejected under 35 U.S.C. 102(b) as being anticipated by Hong et al. (WO 02/08447 A2).

Regarding claim 18, Hong teaches an oligonucleotide comprising the instant SEQ ID 2 (see SEQ ID NO: 5 on page 23 of Hong and the alignment below). Hong teaches that this oligonucleotide is suitable for use in amplification reaction (see page 23).

```
Qy          1 GCAGTACCACAAGGCCTTTCGC 22
              ||||||||||||||||||||||
Db          8 GCAGTACCACAAGGCCTTTCGC 29
```

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 19 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weimer et al. (US 6,248,526 B1) in view of Hong et al. (WO 02/08447 A2).

The teachings of Weimer and Hong are discussed above. The teachings of Weimer anticipate the instant claims 16, 18, 22, 23, 25, and 29. The teachings of Hong anticipate the instant claim 18.

Regarding claims 19 and 24, Weimer teaches a primer specific to the 5' noncoding region of HCV-1 that comprises the instant SEQ ID NO: 3, as discussed above (see Example 1, column 6, lines 1-29 and SEQ ID NO: 1 of Weimer). As noted above, SEQ ID NO: 1 of Weimer comprises the instant SEQ ID NO: 3.

Weimer does not teach a primer pair comprising the instant SEQ ID NO: 2 and SEQ ID NO: 3 as required by claims 19 and 24.

Hong teaches a primer comprising the instant SEQ ID NO: 2 for amplification of HCV (see page 23, as discussed in greater detail above, where SEQ ID NO: 5 comprises the instant SEQ ID NO: 2).

Hong does not teach a primer pair comprising SEQ ID NO: 2 and SEQ ID NO: 3.

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to obtain a primer pair comprising an oligonucleotide of SEQ ID NO: 2 and an oligonucleotide of SEQ ID NO: 3. As discussed above, Weimer taught that a primer comprising SEQ ID NO: 3 was useful for amplifying HCV, and Hong taught that a primer comprising SEQ ID NO: 2 was useful for amplifying HCV. Therefore, an ordinary practitioner would have been motivated to use these sequences together as a primer pair for specific amplification of HCV. As noted in MPEP 2144.07, selection of known materials based on their suitability for the intended

use is prima facie obvious. An ordinary practitioner also would have been motivated to additionally include in the kit of Weimer any primers known to be useful for HCV amplification in order to obtain the ability to amplify different regions of the virus. Since Hong taught that a primer comprising the instant SEQ ID NO: 2 was useful for amplifying HCV (see page 23), an ordinary practitioner would have been motivated to further include this primer in the kit of Weimer in order to obtain the ability to amplify another region of HCV. An ordinary practitioner would have had a reasonable expectation of success in doing so, since the primer taught by Hong could be synthesized using standard procedures. Thus, the primer pair of claim 19 and the kit of claim 24 are prima facie obvious in view of the combined teachings of Weimer and Hong.

11. Claim 20 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bukh et al. (Proceedings of the National Academy of Sciences, USA (1992) 89(11): 4942-4946; cited on IDS) in view of Watanabe et al. (Journal of Microbiological Methods (2001) 44: 253-262) and further in view of Heid et al. (Genome Research (1996) 6(10): 986-994).

Bukh teaches the nucleic acid sequence of the 5' noncoding region of HCV (see Figure 1). Regarding claim 20, in Figure 1, Bukh teaches the prototype HCV-1 sequence of the 5' noncoding region. The complement of nucleotides –93 to –69 in this sequence is highly similar to the claimed SEQ ID NO: 6 (see alignment below).

```
Bukh          -69 CGCGACCCAACACTACTCGGCTAGC -93
                  ||| ||||||| ||||| ||||||
SEQ ID NO: 6    1 CGCIACCCAACICTACTIGGCTAGT  25
```

Bukh also aligned the prototype HCV-1 sequence for the 5' noncoding region with 44 other HCV sequences (see Figure 1). Bukh expressly stated that the alignment is useful for design of oligonucleotide primers (page 4946, column 2). However, Bukh does not teach an isolated oligonucleotide comprising the claimed probe with inosine substitution at the above positions. Bukh also does not teach dual labeling of the probe with FAM and TAMRA.

Watanabe teaches universal primers for amplification of bacterial sequences (see abstract and page 258). Regarding claim 20, Watanabe teaches that introduction of deoxyinosine at positions where nucleotide mismatches occur between the different target sequences (see page 258). Watanabe teaches that inosine substitution neutralizes the effect of these substitutions on the hybridization properties of oligonucleotide probes (page 258).

Watanabe does not teach a probe doubly labeled with FAM and TAMRA.

Heid teaches methods for quantitative real-time PCR detection. The method of Heid comprises inclusion of an oligonucleotide probe labeled at the 5' end with FAM and the 3' end with TAMRA in a PCR reaction (page 987, column 2 and page 993, column 1). Heid teaches that during PCR amplification, the probe hybridizes to the amplified product (page 987, column 2). When this product is used as a template for further amplification, the quencher (TAMRA) is cleaved from the probe by the exonuclease activity of the polymerase resulting in an increase in fluorescence signal proportional to amplicon production (page 987, column 2). Heid teaches that PCR product accumulation can be accurately and reproducibly measured in real time by quantifying this fluorescence (see abstract, page 987, column 1, and pages 991-992).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to synthesize a probe comprising SEQ ID NO: 6. An ordinary practitioner would have

been motivated to synthesize an oligonucleotide probe comprising any stretch of nucleic acids shown in Figure 1 of Bukh for specific detection of HCV nucleic acids. For universal detection of many different HCV nucleic acids, an ordinary practitioner would have been motivated to design the probe from any region shown in the alignment of Bukh to contain a high degree of conservation (e.g. the region comprising positions –93 to –69). As discussed above, Bukh expressly suggested designing oligonucleotides, such as primers, from the conserved regions of the 5' noncoding sequence (page 4946). An ordinary practitioner also would have been motivated to substitute inosine at those nucleotide positions where variability was observed, since Wantanabe taught that inosine substitution neutralized these sequence differences, thereby permitting universal detection of many sequences (page 258). An ordinary practitioner would have been motivated to substitute inosine at the claimed positions in SEQ ID NO: 6, since the alignment of Bukh showed sequence variability at these positions (see Figure 1). Finally, an ordinary practitioner would have been motivated to label the probe with FAM and TAMRA to permit its use in quantitative real-time PCR as suggested by Heid.

Attention is also directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.____, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at ____, 82 USPQ2d at 1397)."

In the instant case, as discussed above, an ordinary practitioner would have been motivated to design a probe from any stretch of nucleotides in the known HCV-1 5' noncoding

region for detection of HCV. Bukh's disclosure of the nucleic acid sequence of the 5' non-coding region of HCV-1 in Figure 1 presented the ordinary artisan with a finite number of possible probes. Bukh further limited the choices for probe design by aligning the 5' non-coding region of the prototype HCV-1 sequence with 44 other HCV sequences (Figure 1), thereby identifying the conserved and variable regions. This alignment also expressly suggested the positions that should be substituted with deoxyinosine to permit universal detection. Since oligonucleotide synthesis and labeling methods were well known in the art, an ordinary practitioner would have expected predictable results, and thus would have had a reasonable expectation of success, when designing and synthesizing the finite number of possible probes suggested by the prior art of Bukh, Watanabe, and Heid. Thus, the probe of claim 20 is prima facie obvious in view of the combined teachings of Bukh, Watanabe, and Heid in the absence of secondary considerations.

12. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weimer (US 6,248,526 B1) in view of Bukh et al. (Proceedings of the National Academy of Sciences, USA (1992) 89(11): 4942-4946; cited on IDS) in view of Watanabe et al. (Journal of Microbiological Methods (2001) 44: 253-262) and further in view of Buck et al. (Biotechniques (1999) 27(3): 528-536).

The teachings of Weimer anticipate the products of claims 16, 18, 23, 25, and 29, as discussed above.

Weimer does not teach inclusion of a primer comprising the instant SEQ ID NO: 1 in the kit of claim 16.

Bukh teaches the nucleic acid sequence of the 5' noncoding region of HCV (see Figure 1). Regarding claim 27, in Figure 1, Bukh teaches the prototype HCV-1 sequence of the 5' noncoding region. Nucleotides –134 to –118 in this sequence are highly similar to the claimed SEQ ID NO: 1 with the exception of the inosine in the instantly claimed sequence (see below).

```
Bukh          -134 CCGCTCAATGCCTGGAG -118
                   || ||||||||||||||||
SEQ ID NO: 1   1 CCICTCAATGCCTGGAG  17
```

Bukh also aligned the prototype HCV-1 sequence for the 5' noncoding region with 44 other HCV sequences (see Figure 1). Bukh expressly stated that the alignment is useful for design of oligonucleotide primers (page 4946, column 2). However, Bukh does not teach primer comprising SEQ ID NO: 1 with an inosine substitution at the third nucleotide.

Watanabe teaches universal primers for amplification of bacterial sequences (see abstract and page 258). Regarding claim 27, Watanabe teaches that introduction of deoxyinosine at positions where nucleotide mismatches occur between the different target sequences (see page 258). Watanabe teaches that inosine substitution neutralizes the effect of these substitutions on the hybridization properties of oligonucleotide probes (page 258).

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever

failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that the selection and use of primers in primer extension methods yields predictable results.

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to further include a primer comprising SEQ ID NO: 1 in the kit taught by Weimer. An ordinary practitioner would have been motivated to further include any HCV-specific primer in the kit of Weimer in order to obtain the ability to amplify different regions of the virus. An ordinary practitioner would have been motivated to design a primer from the 5' noncoding sequence presented in Figure 1 since Bukh expressly suggested using the alignment for primer design (page 4946). An ordinary practitioner also would have been motivated to substitute inosine at those nucleotide positions where variability was observed, since Wantanabe taught that inosine substitution neutralized these sequence differences, thereby permitting universal detection of many sequences (page 258). An ordinary practitioner would have been motivated to substitute inosine at the third nucleotide in SEQ ID NO: 1, since the alignment of Bukh showed sequence variability at this position (see Figure 1). Since Buck clearly demonstrated the equivalence of primer sequences, an ordinary biochemist would have anticipated a reasonable

level of success in designing and using any extension primer designed from the sequence taught by Bukh to specifically amplify and detect HCV.

Attention is also directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.____, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at ____, 82 USPQ2d at 1397)."

In the instant case, as discussed above, an ordinary practitioner would have been motivated to design a primer from any stretch of nucleotides in the known HCV-1 5' noncoding region for detection of HCV. Bukh's disclosure of the nucleic acid sequence of the 5' non-coding region of HCV-1 in Figure 1 presented the ordinary artisan with a finite number of possible primers. Bukh further limited the choices for probe design by aligning the 5' non-coding region of the prototype HCV-1 sequence with 44 other HCV sequences (Figure 1), thereby identifying the conserved and variable regions. This alignment also expressly suggested the positions that should be substituted with deoxyinosine to permit universal detection. Since Buck taught that a large number of primers designed to detect the same target functioned reasonably well (see above), an ordinary practitioner would have expected predictable results, and thus would have had a reasonable expectation of success, when testing the finite number of possible amplification primers suggested by the prior art of Bukh and Watanabe. Thus, the kit of claim 27 is prima facie obvious in view of the combined teachings of Weimer, Bukh, Watanabe, and Buck in the absence of secondary considerations.

13. Claims 19 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weimer (US 6,248,526 B1) in view of Bukh et al. (Proceedings of the National Academy of Sciences, USA (1992) 89(11): 4942-4946; cited on IDS) in view of Watanabe et al. (Journal of Microbiological Methods (2001) 44: 253-262) and further in view of Buck et al. (Biotechniques (1999) 27(3): 528-536) and further in view of Hong et al. (WO 02/08447 A2).

The teachings of Weimer anticipate the products of claims 16, 18, 23, 25, and 29, as discussed above.

The combined teachings of Weimer, Bukh, Watanabe, and Buck result in the kit of claim 27, as discussed above.

Regarding claim 19, the combined teachings of Bukh and Watanabe suggest a primer comprising SEQ ID NO: 1, as discussed in the previous section.

None of the above references (Weimer, Bukh, Watanabe, Buck) teaches inclusion of a primer comprising SEQ ID NO: 2 in the kit or a primer pair comprising SEQ ID NO: 1 and 2.

Regarding claims 19 and 28, Hong teaches a primer comprising the instant SEQ ID NO: 2 for amplification of HCV (see page 23, as discussed in greater detail above, where SEQ ID NO: 5 comprises the instant SEQ ID NO: 2).

Hong does not teach a primer pair comprising SEQ ID NO: 1 and SEQ ID NO: 2.

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to obtain a primer pair comprising an oligonucleotide of SEQ ID NO: 1 and an oligonucleotide of SEQ ID NO: 2. As discussed in the previous section, the combined teachings of Bukh and Watanabe suggest a primer comprising SEQ ID NO: 1 for amplification of HCV. Also, as discussed above, Hong taught that a primer comprising SEQ ID NO: 2 was useful for

amplifying HCV. Therefore, an ordinary practitioner would have been motivated to use oligonucleotides sequences together as a primer pair for specific amplification of HCV. As noted in MPEP 2144.07, selection of known materials based on their suitability for the intended use is prima facie obvious. An ordinary practitioner also would have been motivated to additionally include in the kit resulting from the combined teachings of Weimer, Bukh, and Watanabe any primers known to be useful for HCV amplification in order to obtain the ability to amplify different regions of the virus. Since Hong taught that a primer comprising the instant SEQ ID NO: 2 was useful for amplifying HCV (see page 23), an ordinary practitioner would have been motivated to further include this primer in the kit resulting from the combined teachings of Weimer, Bukh, and Watanabe in order to obtain the ability to amplify another region of HCV. An ordinary practitioner would have had a reasonable expectation of success in doing so, since the primer taught by Hong could be synthesized using standard procedures. Thus, the primer pair of claim 19 and the kit of claim 28 are prima facie obvious in view of the combined teachings of Weimer, Bukh, Watanabe, Buck, and Hong.

14. Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weimer (US 6,248,526 B1) in view of Bukh et al. (Proceedings of the National Academy of Sciences, USA (1992) 89(11): 4942-4946; cited on IDS) in view of Watanabe et al. (Journal of Microbiological Methods (2001) 44: 253-262) and further in view of Heid et al. (Genome Research (1996) 6(10): 986-994).

The teachings of Weimer anticipate the products of claims 16, 18, 23, 25, and 29, as discussed above.

Weimer does not teach inclusion of a probe comprising SEQ ID NO: 6 in the kit.

Bukh teaches the nucleic acid sequence of the 5' noncoding region of HCV (see Figure 1). Regarding claim 30, in Figure 1, Bukh teaches the prototype HCV-1 sequence of the 5' noncoding region. The complement of nucleotides –93 to –69 in this sequence is highly similar to the claimed SEQ ID NO: 6 (see alignment below).

```
Bukh          -69 CGCGACCCAACACTACTCGGCTAGC -93
                  ||| ||||||| ||||| ||||||
SEQ ID NO: 6    1 CGCIACCCAACICTACTIGGCTAGT  25
```

Bukh also aligned the prototype HCV-1 sequence for the 5' noncoding region with 44 other HCV sequences (see Figure 1). Bukh expressly stated that the alignment is useful for design of oligonucleotide primers (page 4946, column 2). However, Bukh does not teach an isolated oligonucleotide comprising the claimed probe with inosine substitution at the above positions. Bukh also does not teach dual labeling of the probe with FAM and TAMRA.

Watanabe teaches universal primers for amplification of bacterial sequences (see abstract and page 258). Regarding claim 30, Watanabe teaches that introduction of deoxyinosine at positions where nucleotide mismatches occur between the different target sequences (see page 258). Watanabe teaches that inosine substitution neutralizes the effect of these substitutions on the hybridization properties of oligonucleotide probes (page 258).

Watanabe does not teach a probe doubly labeled with FAM and TAMRA.

Heid teaches methods for quantitative real-time PCR detection. The method of Heid comprises inclusion of an oligonucleotide probe labeled at the 5' end with FAM and the 3' end with TAMRA in a PCR reaction (page 987, column 2 and page 993, column 1). Heid teaches that during PCR amplification, the probe hybridizes to the amplified product (page 987, column

2). When this product is used as a template for further amplification, the quencher (TAMRA) is cleaved from the probe by the exonuclease activity of the polymerase resulting in an increase in fluorescence signal proportional to amplicon production (page 987, column 2). Heid teaches that PCR product accumulation can be accurately and reproducibly measured in real time by quantifying this fluorescence (see abstract, page 987, column 1, and pages 991-992).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to synthesize a probe comprising SEQ ID NO: 6 and include this oligonucleotide probe in the kit taught by Weimer. An ordinary practitioner would have been motivated to synthesize an oligonucleotide probe comprising any stretch of nucleic acids shown in Figure 1 of Bukh for specific detection of HCV nucleic acids. For universal detection of many different HCV nucleic acids, an ordinary practitioner would have been motivated to design the probe from any region shown in the alignment of Bukh to contain a high degree of conservation (e.g. the region comprising positions –93 to –69). As discussed above, Bukh expressly suggested designing oligonucleotides, such as primers, from the conserved regions of the 5' noncoding sequence (page 4946). An ordinary practitioner also would have been motivated to substitute inosine at those nucleotide positions where variability was observed, since Wantanabe taught that inosine substitution neutralized these sequence differences, thereby permitting universal detection of many sequences (page 258). An ordinary practitioner would have been motivated to substitute inosine at the claimed positions in SEQ ID NO: 6, since the alignment of Bukh showed sequence variability at these positions (see Figure 1). Finally, an ordinary practitioner would have been motivated to label the probe with FAM and TAMRA to permit its use in quantitative real-time PCR as suggested by Heid. Since the kits taught by Weimer were designed to provide reagents

for amplification and detection of HCV (column 5, lines 50-60 and column 6, lines 1-29), an ordinary practitioner would have been especially motivated to include the probe resulting from the combined teachings of Bukh, Watanabe, and Heid in the kit of Weimer to permit accurate, reproducible, and real-time detection of PCR products generated using the kit components.

Lastly, attention is directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.____, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at ____, 82 USPQ2d at 1397)."

In the instant case, as discussed above, an ordinary practitioner would have been motivated to design a probe from any stretch of nucleotides in the known HCV-1 5' noncoding region for detection of HCV. Bukh's disclosure of the nucleic acid sequence of the 5' non-coding region of HCV-1 in Figure 1 presented the ordinary artisan with a finite number of possible probes. Bukh further limited the choices for probe design by aligning the 5' non-coding region of the prototype HCV-1 sequence with 44 other HCV sequences (Figure 1), thereby identifying the conserved and variable regions. This alignment also expressly suggested the positions that should be substituted with deoxyinosine to permit universal detection. Since oligonucleotide synthesis and labeling methods were well known in the art, an ordinary practitioner would have expected predictable results, and thus would have had a reasonable expectation of success, when designing and synthesizing the finite number of possible probes suggested by the prior art of Bukh, Watanabe, and Heid. Thus, design of a probe comprising

SEQ ID NO: 6 for inclusion in the kit taught by Weimer is prima facie obvious in view of the combined teachings of Bukh, Watanabe, and Heid in the absence of secondary considerations.

15. Claims 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weimer (US 6,248,526 B1) in view of Bukh et al. (Proceedings of the National Academy of Sciences, USA (1992) 89(11): 4942-4946; cited on IDS) and further in view of Tyagi et al. (US 6,037,130) and further in view of Buck et al. (Biotechniques (1999) 27(3): 526-538).

The teachings of Weimer anticipate the products of claims 16, 18, 23, 25, and 29, as discussed above.

Weimer does not teach inclusion of a molecular beacon primer comprising SEQ ID NO: 7 in the kit.

Bukh teaches the nucleic acid sequence of the 5' noncoding region of HCV (see Figure 1). Regarding claims 31 and 32, in Figure 1, Bukh teaches the prototype HCV-1 sequence of the 5' noncoding region. Nucleotides –134 to –118 in this sequence are highly similar to the 3' region of the claimed SEQ ID NO: 7 (see below).

```
Bukh          -134 CCGCTCAATGCCTGGAG -118
                   |||||||||||||||||
SEQ ID NO: 7       CCGCTCAATGCCTGGAG
```

Bukh also aligned the prototype HCV-1 sequence for the 5' noncoding region with 44 other HCV sequences (see Figure 1). Bukh expressly stated that the alignment is useful for design of oligonucleotide primers (page 4946, column 2). However, Bukh does not teach primer comprising SEQ ID NO: 7.

Tyagi teaches wavelength-shifting molecular beacon primers (column 2, lines 29-44). Regarding claims 31 and 32, the hairpin region of the molecular beacon primer taught by Tyagi exactly matches the 5' portion of the claimed sequence (see column 18, where SEQ ID NO: 12 of Tyagi contains the sequence 5'-FAM-caccttcaccctcagaagg-DABCYL-g). Tyagi further teaches that the DABCYL quencher may be substituted with methyl red (column 5, lines 32-36). Tyagi teaches that the wavelength-shifting molecular beacon primers produce a greater signal and less background noise than conventional hairpin primers (column 2, lines 1-21).

Buck analyzed the effect of primer design strategy on the performance of DNA sequencing primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that every single primer worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, every single control primer functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This

clearly shows that the selection and use of primers in primer extension methods yields predictable results.

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to further include a primer comprising SEQ ID NO: 7 in the kit taught by Weimer. An ordinary practitioner would have been motivated to further include any HCV-specific primer in the kit of Weimer in order to obtain the ability to amplify different regions of the virus. An ordinary practitioner would have been motivated to design a primer from the 5' noncoding sequence presented in Figure 1 since Bukh expressly suggested using this alignment for primer design (page 4946). An ordinary practitioner also would have been motivated by the teachings of Tyagi to construct a wavelength-shifting molecular beacon primer using the hairpin forming sequence taught by Tyagi in order to obtain a primer capable of generating a large fluorescence signal with minimal background for use in multiplex real-time amplification assays. Combination of the hairpin forming region taught by Tyagi and the HCV-specific portion suggested by Bukh would result in the primer of SEQ ID NO: 7. Since the kits taught by Weimer were designed to provide reagents for amplification and detection of HCV (column 5, lines 50-60 and column 6, lines 1-29), an ordinary practitioner would have been especially motivated to include the primer resulting from the combined teachings of Bukh and Tyagi in the kit of Weimer to permit accurate, reproducible, and real-time detection of PCR products generated using the kit components. An ordinary practitioner would have had a reasonable expectation of success in designing and using this primer since synthesis and labeling methods were well known in the art, and also since Buck clearly demonstrated the equivalence of primer sequences.

Finally, attention is directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.____, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at ____, 82 USPQ2d at 1397)."

In the instant case, as discussed above, an ordinary practitioner would have been motivated to design a primer from any stretch of nucleotides in the known HCV-1 5' noncoding region for detection of HCV. Bukh's disclosure of the nucleic acid sequence of the 5' non-coding region of HCV-1 in Figure 1 presented the ordinary artisan with a finite number of possible primers. Bukh further limited the choices for probe design by aligning the 5' non-coding region of the prototype HCV-1 sequence with 44 other HCV sequences (Figure 1), thereby identifying the conserved and variable regions. Since Buck taught that a large number of primers designed to detect the same target functioned reasonably well (see above), an ordinary practitioner would have expected predictable results, and thus would have had a reasonable expectation of success, when testing the finite number of possible amplification primers suggested by the prior art of Bukh and Tyagi. Thus, the kits of claims 31 and 32 are prima facie obvious in view of the combined teachings of Weimer, Bukh, Tyagi, and Buck in the absence of secondary considerations.

16. Claims 19 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weimer (US 6,248,526 B1) in view of Bukh et al. (Proceedings of the National Academy of Sciences,

USA (1992) 89(11): 4942-4946; cited on IDS) and further in view of Tyagi et al. (US 6,037,130) and further in view of Buck et al. (Biotechniques (1999) 27(3): 526-538) and further in view of Hong et al. (WO 02/08447 A2).

The teachings of Weimer anticipate the products of claims 16, 18, 23, 25, and 29, as discussed above.

The combined teachings of Weimer, Bukh, Tyagi, and Buck result in the kit of claims 31 and 32, as discussed above.

Regarding claim 19, the combined teachings of Bukh and Tyagi suggest a primer comprising SEQ ID NO: 7, as discussed in the previous section.

None of the above references (Weimer, Bukh, Tyagi, Buck) teaches inclusion of a primer comprising SEQ ID NO: 2 in the kit or a primer pair comprising SEQ ID NO: 2 and 7.

Regarding claims 19 and 33, Hong teaches a primer comprising the instant SEQ ID NO: 2 for amplification of HCV (see page 23, as discussed in greater detail above, where SEQ ID NO: 5 comprises the instant SEQ ID NO: 2).

Hong does not teach a primer pair comprising SEQ ID NO: 7 and SEQ ID NO: 2.

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to obtain a primer pair comprising an oligonucleotide of SEQ ID NO: 7 and an oligonucleotide of SEQ ID NO: 2. As discussed in the previous section, the combined teachings of Bukh and Tyagi suggested a primer comprising SEQ ID NO: 7 for amplification of HCV. Also, as discussed above, Hong taught that a primer comprising SEQ ID NO: 2 was useful for amplifying HCV. Therefore, an ordinary practitioner would have been motivated to use these two oligonucleotide sequences together as a primer pair for specific amplification of HCV. As

noted in MPEP 2144.07, selection of known materials based on their suitability for the intended use is prima facie obvious. An ordinary practitioner also would have been motivated to additionally include in the kit resulting from the combined teachings of Weimer, Bukh, Tyagi, and Buck any primers known to be useful for HCV amplification in order to obtain the ability to amplify different regions of the virus. Since Hong taught that a primer comprising the instant SEQ ID NO: 2 was useful for amplifying HCV (see page 23), an ordinary practitioner would have been motivated to further include this primer in the kit resulting from the combined teachings of Weimer, Bukh, Tyagi, and Buck in order to obtain the ability to amplify another region of HCV. An ordinary practitioner would have had a reasonable expectation of success in doing so, since the primer taught by Hong could be synthesized using standard procedures. Thus, the primer pair of claim 19 and the kit of claim 33 are prima facie obvious in view of the combined teachings of Weimer, Bukh, Tyagi, Buck, and Hong.

17. Claim 35 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bukh et al. (Proceedings of the National Academy of Sciences, USA (1992) 89(11): 4942-4946; cited on IDS) in view of Tyagi et al. (US 6,037,130).

Bukh teaches the nucleic acid sequence of the 5' noncoding region of HCV (see Figure 1). Regarding claim 35, in Figure 1, Bukh teaches the prototype HCV-1 sequence of the 5' noncoding region. Nucleotides –134 to –118 in this sequence are highly similar to the 3' region of the claimed SEQ ID NO: 7 (see below).

```
Bukh          -134 CCGCTCAATGCCTGGAG -118
                   |||||||||||||||||
SEQ ID NO: 7       CCGCTCAATGCCTGGAG
```

Bukh also aligned the prototype HCV-1 sequence for the 5' noncoding region with 44 other HCV sequences (see Figure 1). Bukh expressly stated that the alignment is useful for design of oligonucleotide primers (page 4946, column 2). However, Bukh does not teach an oligonucleotide comprising SEQ ID NO: 7.

Tyagi teaches wavelength-shifting molecular beacon primers (column 2, lines 29-44). Regarding claim 35, the hairpin region of the molecular beacon primer taught by Tyagi exactly matches the 5' portion of the claimed sequence (see column 18, where SEQ ID NO: 12 of Tyagi contains the sequence 5'-FAM-caccttcaccctcagaagg-DABCYL-g). Tyagi further teaches that the DABCYL quencher may be substituted with methyl red (column 5, lines 32-36). Tyagi teaches that the wavelength-shifting molecular beacon primers produce a greater signal with less background noise than conventional hairpin primers (column 2, lines 1-21).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to synthesize an oligonucleotide comprising SEQ ID NO: 7. An ordinary practitioner would have been motivated to design an oligonucleotide from any portion of the 5' noncoding sequence presented in Figure 1 since Bukh expressly suggested using this sequence alignment for primer design (page 4946). An ordinary practitioner also would have been motivated by the teachings of Tyagi to construct a wavelength-shifting molecular beacon primer using the hairpin forming sequence taught by Tyagi in order to obtain a primer capable of generating a large fluorescence signal with minimal background for use in multiplex real-time amplification assays. Combination of the hairpin forming region taught by Tyagi and the HCV-specific portion suggested by Bukh would result in the primer of SEQ ID NO: 7. An ordinary practitioner would

have had a reasonable expectation of success in designing an oligonucleotide of SEQ ID NO: 7 since synthesis and labeling methods were well known in the art.

Finally, attention is directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.____, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at ____, 82 USPQ2d at 1397)."

In the instant case, as discussed above, an ordinary practitioner would have been motivated to design an oligonucleotide from any stretch of nucleotides in the known HCV-1 5' noncoding region for detection of HCV. Bukh's disclosure of the nucleic acid sequence of the 5' non-coding region of HCV-1 in Figure 1 presented the ordinary artisan with a finite number of possible oligonucleotides. Bukh further limited the choices for probe design by aligning the 5' non-coding region of the prototype HCV-1 sequence with 44 other HCV sequences (Figure 1), thereby identifying the conserved and variable regions. Therefore, an ordinary practitioner would have expected predictable results, and thus would have had a reasonable expectation of success, when testing the finite number of possible amplification primers suggested by the prior art of Bukh and Tyagi. Thus, the oligonucleotide of claim 35 is prima facie obvious in view of the combined teachings of Bukh and Tyagi in the absence of secondary considerations.

18. Claim 36 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weimer in view of Bukh et al. (Proceedings of the National Academy of Sciences, USA (1992) 89(11): 4942-

4946; cited on IDS) in view of Tyagi et al. (US 6,037,130) and further in view of Hong et al. (WO 02/08447 A2).

The combined teachings of Bukh and Tyagi result in the oligonucleotide of claim 35, as discussed above.

Regarding claim 36, Tyagi teaches inclusion of the wavelength-shifting molecular beacon primers in kits (see claims 1, 13, and 22, for example).

Neither Bukh nor Tyagi teaches inclusion of a primer comprising SEQ ID NO: 2 in the kit.

Regarding claim 36, Hong teaches a primer comprising the instant SEQ ID NO: 2 for amplification of HCV (see page 23, as discussed in greater detail above, where SEQ ID NO: 5 comprises the instant SEQ ID NO: 2).

It would have been prima facie obvious for one of ordinary skill in the art at the time of invention to include a primer of SEQ ID NO: 2 in the kit resulting from the combined teachings of Bukh and Tyagi. An ordinary practitioner would have been motivated to include in the kit taught by Tyagi any primers known to be useful for amplification in order to obtain the ability to amplify different target nucleic acids. Since Hong taught that a primer comprising the instant SEQ ID NO: 2 was useful for amplifying HCV (see page 23), an ordinary practitioner would have been motivated to further include this primer in the kit resulting from the combined teachings of Bukh and Tyagi. An ordinary practitioner would have had a reasonable expectation of success in doing so, since the primer taught by Hong could be synthesized using standard procedures. Thus, the kit of claim 36 is prima facie obvious in view of the combined teachings of Bukh, Tyagi, and Hong.

Conclusion

No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Angela Bertagna
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August 29, 2007

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8/29/07